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Contract Concept Review:
Investigative absorption, distribution, metabolism and
excretion (ADME) studies of toxicants in NTP animal
model systems

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Introduction

- General information regarding ADME studies conducted by NIEHS
- Host Susceptibility Branch overview (selection of NTP animal model systems)
- Proof-of-Principle study - Benzene



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Contract Support for ADME Studies

- Perform ADME studies for NTP designated chemicals in multiple species and genetically defined strains of those species and in genetically-modified animal models in order to identify polymorphic genetic loci that influence ADME pathways and toxicity outcomes



History

Productivity on Chemical Disposition in Mammals Contract since 1978:

- Approximately 100 peer reviewed publications
- Training activities in Toxicology 11 M.S. degrees; 15 Ph.D. degrees; 16 postdoctoral fellows



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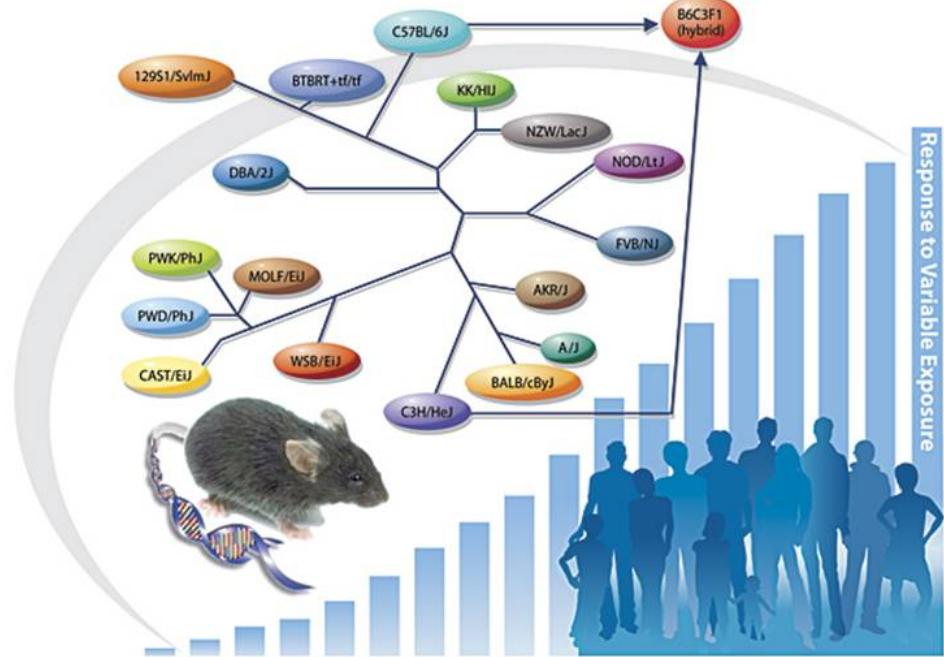
Background - ADME

- Absorption
- Distribution (Tissue)
- Metabolism
- Excretion
- Mass Balance
- What does the animal do to the chemical?



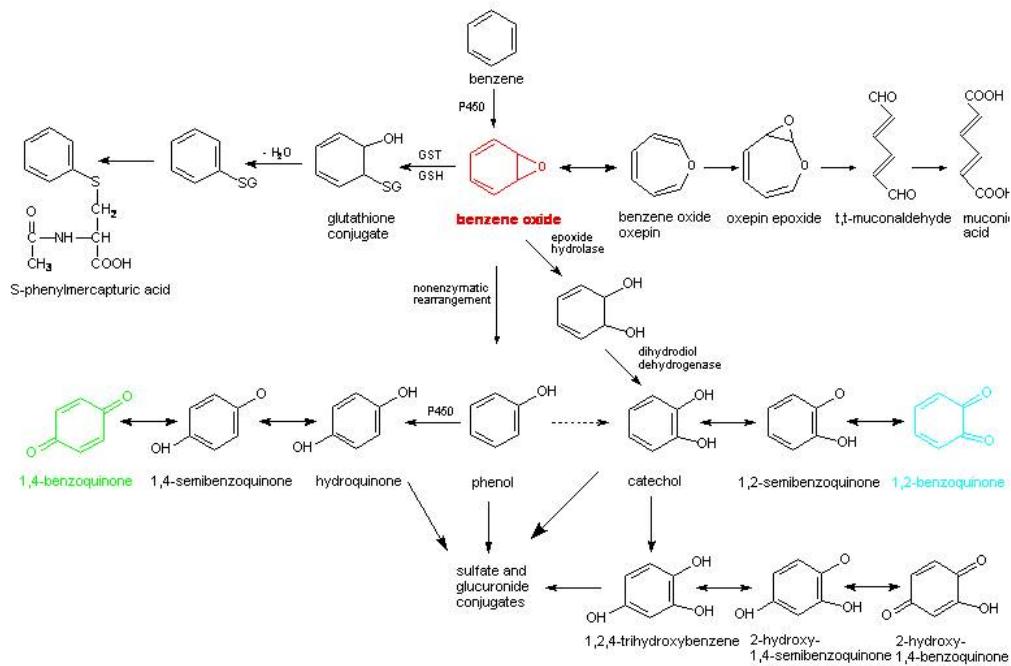
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HOST SUSCEPTIBILITY BRANCH



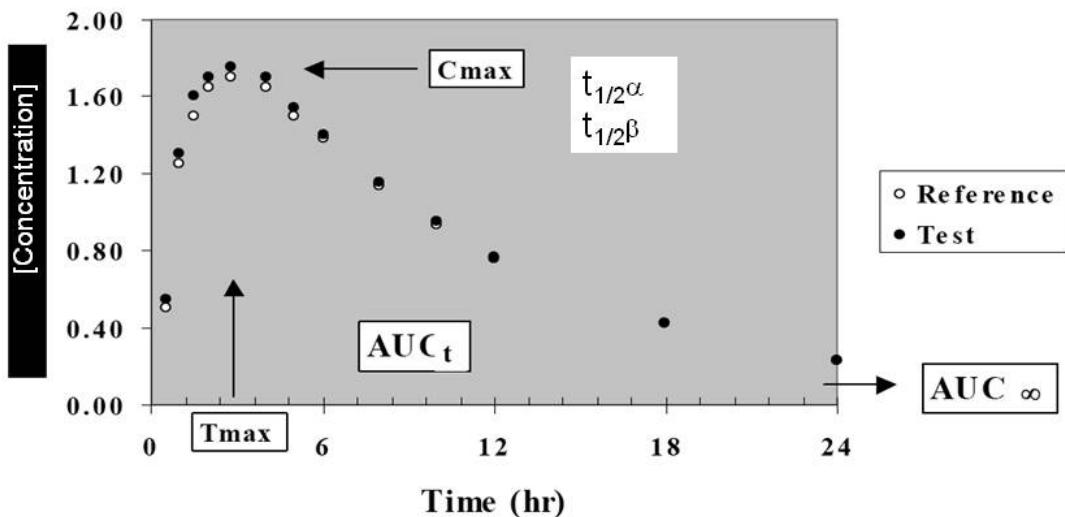


Benzene Metabolism



Type of Data Collected

Mean Reference and Test Results



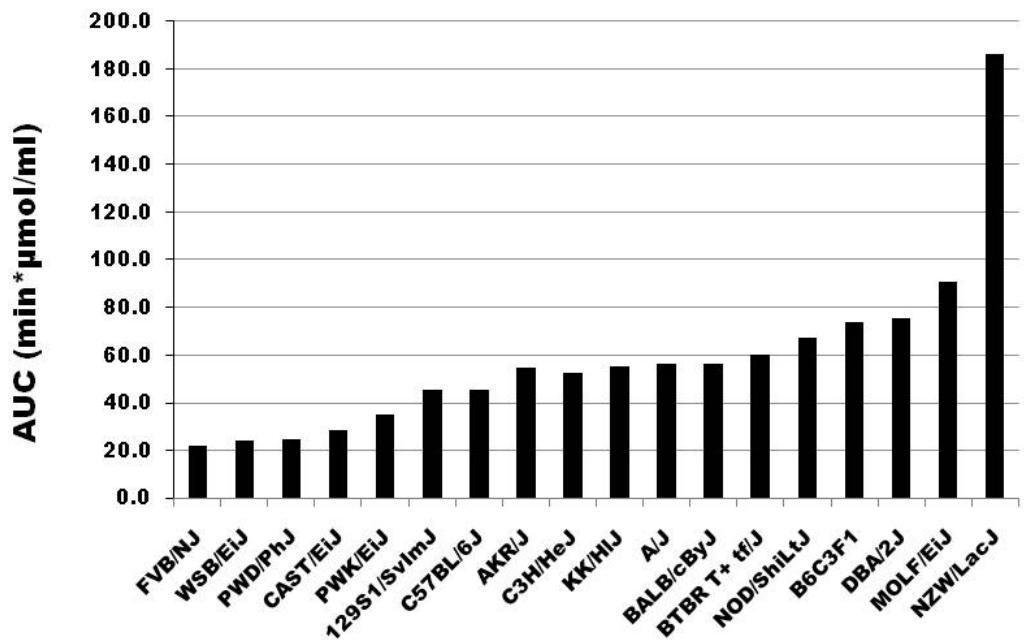


**Summary of Kinetic parameters for [¹⁴C] benzene-equivalents, (sorted by AUC)
following oral administration (100 µg/kg, 75 µCi/kg) in male mice
(Total [¹⁴C] in blood; N=5; WinNonlin v5.2, Pharsight)**

Strain	AUC min*µmol/ml	Cmax nmol/ml	Tmax min	t1/2α min	t1/2β min	CL_F ml/min
NZW/LacJ	186	1360	30	8.8	71	0.12
MOLF/EiJ	90	229	3	0.3	272	0.14
DBA/2J	75	313	10	1.4	160	0.37
B6C3F1	74	294	14	2.2	165	0.30
NOD/ShiLtJ	67	509	4	0.5	88	0.48
BTBR T+tf/J	60	356	11	1.9	108	0.68
BALB/cByJ	56	402	10	1.6	90	0.46
A/J	56	232	3	0.3	166	0.43
KK/Hij	55	749	4	0.7	48	0.55
AKR/J	55	389	18	4.0	84	0.57
C3H/HeJ	52	333	17	3.5	96	0.47
C57BL/6J	45	359	17	3.9	74	0.59
129S1/SvImJ	45	267	15	2.7	106	0.52
PWK/EiJ	35	272	11	1.9	81	0.39
CAST/EiJ	28	226	17	3.8	74	0.82
PWD/PhJ	25	431	11	2.9	31	0.98
WSB/EiJ	24	197	21	5.1	68	0.51
FVB/NJ	22	255	16	4.0	47	0.80

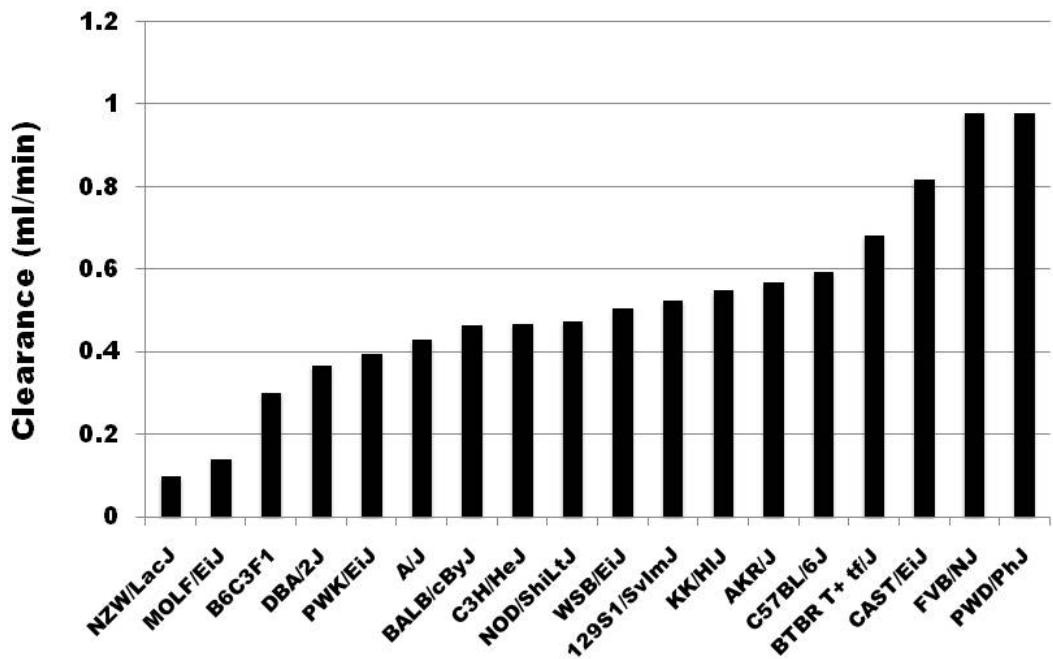


**Rank order [14C] benzene equivalents AUC; min^{*}µmol/ml)
following a single oral exposure (100 µg/kg; N=5)**





**Rank order [14C] benzene equivalents clearance; ml/min)
following a single oral exposure (100 µg/kg; N=5)**





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Summary

- Contract critical to the Host Susceptibility Initiative in selection of NTP animal model systems for future research projects (28-day inhalation study for benzene; additional chemicals)
- Proof-of-Principle study with Benzene demonstrates 10-fold or greater differences in ADME kinetics between strains
- Additional information obtained from ADME in genetically diverse strains is significant for understanding mechanisms of toxicity



Future Directions

- Using the NTP-Perlegen genetic sequence data base of these strains, HSB scientists and collaborators can statistically correlate genome-wide SNP differences with quantitative measures for each strain-specific ADME trait and identify quantitative trait loci or QTL and the candidate gene allelic variants.
- Bioinformatics and functional analysis of the mouse candidate gene allelic variants may then be used to identify human orthologs, which will aid in extrapolation of ADME and toxicity data across species and support functional validation studies in mouse and human cells and tissues.



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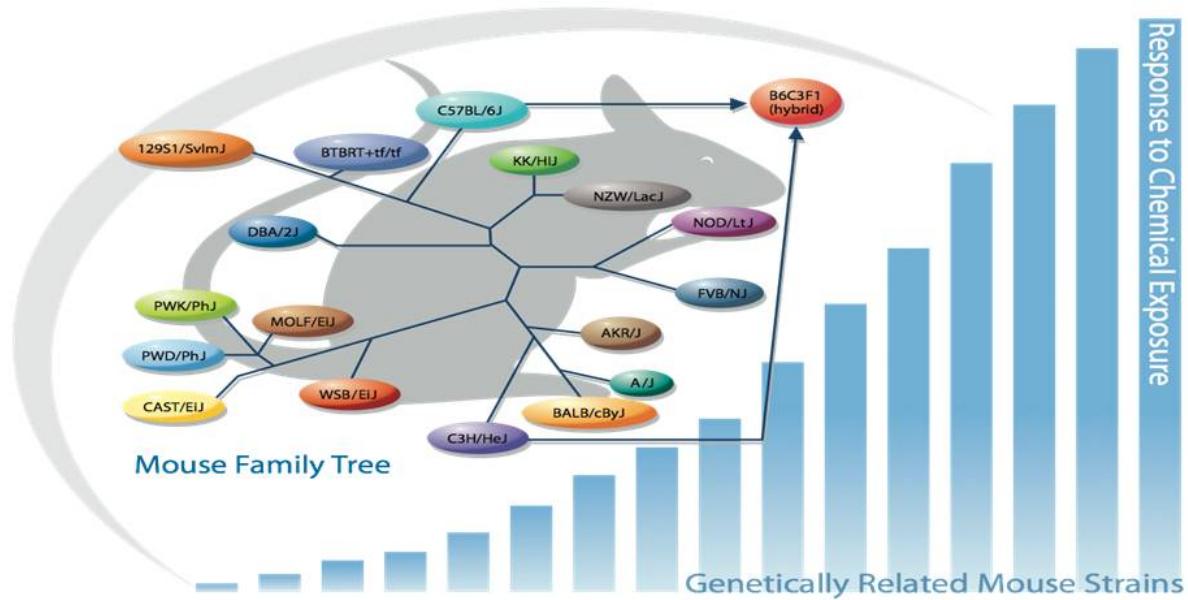


Request

- BSC's approval to conduct ADME studies for the Host Susceptibility Branch in NTP animal model systems via a contract mechanism



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Host Susceptibility Branch